REMARKS

I. Status of the Claims

Claims 1-22 and 24-26 have been canceled, and claim 23 is pending and stands rejected under 35 U.S.C. §112, first paragraph. The specific grounds of rejection, and applicants' responses thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, First Paragraph

Claim 23 stands rejected as lacking an enabling disclosure in the specification. According to the examiner, the specification is defective in (a) failing to provide an adequate basis for predicting that an increase in α-MHC transcripts would benefit subjects having myocardial failure, (b) failing to provide correlation of α-MHC transgene expression *in vivo* with therapeutic benefit, (c) failing to teach or provide guidance with respect to specific levels of α-MHC that would be therapeutic, and (d) failing to teach or provide guidance for delivery of the α-MHC transgene to the heart. Applicants previously provided an extensive response to the examiner's concerns, and for the most part, the examiner has simply "reiterated" the PTO's previous position. Once again, applicants traverse.

First, applicants direct examiner to the enclosed poster abstract from the lab of Jeffrey Robbins, Ph.D., presented at the Keystone Meeting on "Biology of Cardiac Disease" held on March 7, 2004. These data evolved from Robbins' findings on the rabbit heart model presented in James *et al.*, *JMCC* 34, 873-882 (2002). As shown in this abstract, directly supporting the inventor's paradigm and abrogating the examiner's concerns regarding this invention, addition of α-MHC transcripts via a transgenic approach strengthens the heart and renders it resistant to tachycardia induced cardiomyopathy. Moreover, the Robbins' study is highly applicable to the

human setting because Robbins took advantage of the fact that the rabbit heart is constituted much like the human heart, expressing low levels of α-MHC when healthy, and then expressing virtually no α-MHC when the heart is diseased. In this model, if an increase in α-MHC could be shown to be protective, it would be highly predictive for what would be seen in the human heart. This abstract provides direct support for claim 23, showing that adding even as little as 10-15% more α-MHC than baseline is protective to the heart. In other words, and exactly as claimed by the current inventors, adding an α-MHC transgene causes an increase in LVEF directly related to the additional α-MHC expressed in heart tissue.

While this new data alone should be sufficient to overcome the examiner's concerns and enable this claim, applicants will again traverse the examiner's rejection. In the last response applicants supplied the examiner with a variety of references regarding gene therapy, but the examiner focused almost exclusively on the Jones reference, arguing it was not dispositive. The latest rejection ignores the numerous references supplied (and again referenced below) by applicants, reporting on the successful transfer of genes into cardiac tissue. Alexander *et al.*, *Clin. Exp. Pharmacol. Physiol.*, 26:661-668 (1999) reported gene transfer into myocardium through direct injection of plasmid DNA and viral transfer. Chien *et al.*, WO/2000/15821 describe the use of recombinant adenovirus-mediated expression of transgenes in both neonatal and mature cardiac tissues. Other papers reporting cardiac transgene expression included Davidson *et al.*, *Circulation* 104:131 (2001), Pachucki *et al.*, *Endocrinology* 142:13 (2001), Shinmura *et al.*, *Japan Heart J.* 41:633 (2000), Silva *et al.*, *FASEB* 14:1858 (2000), Lenhart *et al.*, *Am. J. Physiol. Heart Circ. Physiol.* 279:H986 (2000), Lazarous *et al.*, *Cardiovasc. Res.* 44:294 (1999), and Wickenden *et al.*, *Circ. Res.* 85:1067 (1999). Interestingly, the examiner again failed to mention those prior submissions.

Additionally, the examiner has now failed to address most of the new references provided in the last response that further undercut the examiner's position on enablement. In particular, the examiner failed to rebut the evidence provided by Yue, Schroeder, O'Donnell, del Monte, and Fromes. Fromes *et al*, *Gene* Therapy, 12:683-688 (1999) described the successful delivery of a gene to the myocardium by intraperitoneal injection. The Fromes paper states that "gene therapy is a potential new strategy for cardiovascular diseases" and adds that "several studies have demonstrated the feasibility of gene transfer into the heart muscle." In addition to Fromes, applicants referenced a number of previous articles that demonstrated the potential of direct injection of genes into the myocardium (*see* Lin *et al*, *Circulation*, 82:2217-2221 (1990); Stratford-Perricaudet *et al*, *J. Clin. Invest.*, 90:626-630 (1992); Von Harsdorf *et al.*, *Circ. Res.*, 72:688-695 (1993); French *et al.*, *Circ. Res.*, 72:688-695 (1993); Lee *et al.*, *J. Thorac. Cardiovasc. Surg.*, 90:2414-2424 (1994); Coffin *et al.*, *Gene Therapy,* 3:560-566 (1996); and Kypson *et al.*, *J. Thorac. Surg.*, 115:623-630 (1998)). Fromes, however, constituted an advance over those reports in developing a technique for "local delivery of the therapeutic gene into the pericardium," demonstrating the successful delivery of a gene to the heart. Fromes' results proved that "intra-pericardial injection ... leads to an efficient and safe strategy to deliver a transgene to the heart." The successful approach taken by Fromes came on the heels of another successful application of cardiovascular gene therapy by Hajjar *et al*, *Proc. Natl. Acad. Sci.*, 95:5251-5256 (1998). Hajjar used a catheter-based technique to successfully alter cardiac function in rat hearts. This study was seen as opening the prospect "of using somatic gene transfer to modulate overall cardiac function *in vivo*."

Applicants then discussed how later researchers built on the success seen by both Fromes and Hajjar, generating additional data that validated the feasibility and effectiveness of

cardiovascular gene therapy. Schroeder *et al.*, *Transplantation*, 70:191-198 (2000) showed that addition of anti-CD4 monoclonal antibodies improved gene transfer into rat cardiac grafts. O'Donnell *et al.*, *Circ. Res.*, 88:415-421 (2001) showed that sarcoplasmic reticulum (SR) ATPase (SERCA), could be expressed in cardiac myocytes. del Monte *et al.*, *Circulation*, 104:1424-1429 (2001) also showed effective transfer of and expression of SERCA2a into a rat heart through adenoviral gene transfer. Li *et al.*, *Gene. Ther.*, 21:1807-1813 (2003) showed that an adenoviral associated vector (AAV) could be successfully used to transfer a reporter gene and a therapeutic gene into the heart of a hamster. Lastly, applicants pointed to Yue *et al.*, *Circulation* (2003), who went yet a step further and actually treated a cardiovascular disease using an AAV vector to deliver a therapeutic gene to the heart of a diseased mouse. Yue not only delivered the gene but was able to see improvement of cardiovascular function and further saw improvement in disease state. The examiner did not address these references in reiterating his objection to cardiac gene therapy. Finally, applicants now direct examiner to the statements of Poller *et al.*, Z Kardiol., 93(3):171-93 (2004), a recent publication exploring cardiac gene therapy approaches. Pollard conclusively states "the important goal of cardiac long-term stability of therapeutic vectors has recently been achieved in animal models using vectors derived from adeno-associated viruses (AAVs)."

Applicants therefore submit that the overwhelming body of evidence in the literature supports gene therapy in the heart as an enabled technology and the present record provides adequate evidence for the value of α-MHC therapy. In response to the examiner's statement that many of the above-cited references are after the date of filing, applicants draw the Examiner's attention to *In re Marzocchi*, 169 USPQ 370 (CCPA 1971), stating that an enablement rejection "can be overcome by suitable proofs indicating that the teaching contained in the specification is

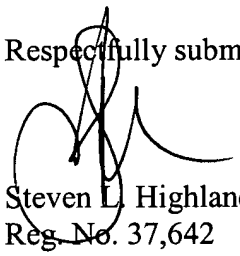
truly enabling." The cited references, coupled with the new abstract by Robbins, are indeed the "suitable proofs" required by the law, and nowhere in the law is it required that these proofs be in the evidentiary record prior to the date of filing.

In short, applicants submit that the present record provides overwhelming evidence of the value of α-MHC therapy. Therefore, reconsideration and withdrawal is respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that the current claim is in condition for allowance, and an early notification to that effect is earnestly solicited. Should Examiner Ton have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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Effects of Ventricular Expression of Alpha Myosin Heavy Chain in Transgenic Rabbits

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The cardiac myosin heavy chain (MHC) isoforms, fast α-MHC and slow β-MHC, are expressed in developmental- and chamber-specific patterns. The mature human ventricle was thought to express only β, but recent reports show that healthy human ventricle contains ~2-10% α-MHC while diseased ventricle has only the β isoform. Because of the intrinsic functional differences between the two isoforms, it has been hypothesized that down-regulation of α-MHC is detrimental and contributes to the failing heart phenotype. Conversely, re-expression of α-MHC may be therapeutic for heart failure. Testing this hypothesis requires the ability to modulate α-MHC levels in an animal with a β-MHC ventricle. These experiments are now possible with the development of transgenic rabbits because the rabbit cardiac MHC expression pattern mimics human. We used the rabbit β-MHC promoter to drive expression of rabbit α-MHC in the heart and obtained four transgenic lines with varying proportions of ventricular α-MHC replacement ranging from ~10-15% (similar to basal human α-MHC levels) to ~50%. The TG animals appear outwardly normal with no difference in growth or longevity compared to NTG littermates up to age 24 months (the oldest rabbits currently available in our colony). Actin activated ATPase rates are increased in TG rabbits to the degree predicted by their α-MHC replacement levels. TG animals show no significant hypertrophy at the cellular or molecular levels. Serial echocardiograms at 4, 8 and >12 months do not demonstrate a hypertrophic response to persistent α-MHC expression and there are no differences between TG and NTG in systolic or diastolic function as assessed by echocardiography and left heart catheterization. We have used these animals in pilot studies to test the hypothesis that persistent α-MHC expression will be protective during tachycardia induced cardiomyopathy (TIC). After a 30 day pacing protocol with sequential increases in ventricular pacing rate, paced TG rabbits showed the expected increase in expression of α-MHC and decrease in β-MHC compared to NTG. Functionally, TG rabbits had a higher shortening fraction (24±2 vs. 20±3, TG vs. NTG, P=.016) and a higher VCFc (1.11±.12 vs. .78±.22, TG vs. NTG, P=.002). We conclude that persistent expression of α-MHC is protective during TIC.